Special Review: Editorial of the POSEIDO PACT

The PACT (Platelet & Advanced Cell Therapies) Forum: fostering translational research, transdisciplinarity and international collaboration in tissue engineering and regenerative medicine

Gilberto Sammartino,[1,*] Marco Del Corso,[2] Lidia M. Wisniewska,[3,4] Tomasz Bielecki,[5] Isabel Andia,[6] Nelson R. Pinto,[7] Chang-Qing Zhang,[8] De-Rong Zou,[9] and David M. Dohan Ehrenfest.[4]

[1] Department of Oral Surgery, Faculty of Medicine, University Federico II of Naples, Italy
[2] Private Practice, Turin, Italy
[3] Department of Didactics and School Organization, Faculty of Education Sciences, University of Granada, Granada, Spain; and Department of International Relations, Paris Sorbonne University, Paris, France
[4] LoB5 research unit, School of Dentistry & Research Center for Biomineralization Disorders, Chonnam National University, Gwangju, South Korea
[5] Department and Clinic of Orthopaedics, Medical University of Silesia, Sosnowiec, Poland
[6] Regenerative Technologies Laboratory, Cruces University Hospital, BioCruces Health Research Institute, Barakaldo, Spain
[7] Department of Surgical and Prosthetic Implantology, Faculty of Odontology, University of the Andes (UANDES), Santiago, Chile
[8] Department of Orthopaedic Surgery, Shanghai Sixth People's Hospital, Shanghai Jiao Tong University, Shanghai, China
[9] Department of Stomatology, Shanghai Sixth People's Hospital, Shanghai Jiao Tong University, China

*Corresponding author: Gilberto Sammartino, gilberto.sammartino@unina.it

Submitted June 6th, 2014; accepted after minor corrections on June 19th, 2014.

Abstract

The PACT (Platelet & Advanced Cell therapies) Forum Civitatis of the POSEIDO was created to offer a multidisciplinary platform of research, publication, debates and eventually consensus for researchers in the fields of Tissue Engineering and Regenerative Medicine (TERM). In this review, the issues, endeavors and perspectives of this considerable research field are discussed and illustrated, particularly (but not only) through the example of the history, failures and success of probably the oldest method developed in regenerative medicine, the topical use of autologous platelet concentrates (commonly known as Platelet-Rich Plasma – PRP or Platelet-Rich Fibrin – PRF). The History of this domain illustrates very well that the greatest enemy of knowledge is not ignorance; it is the illusion of knowledge. Fighting against illusions in Sciences is a very complex and tricky task, requiring continuing efforts and time. This PACT for a transdisciplinary, translational and international approach in regenerative medicine is an important step in this endeavor.

Keywords. Blood platelet, fibrin, growth factors, regenerative medicine, tissue engineering.

1. A multidisciplinary PACT, this is the right TERM

Tissue Engineering and Regenerative Medicine (TERM) is a very active field of research for many medical disciplines **[1]**. The general concept of this domain is to combine cells, scaffold, biological mediators (the 3 main components of a tissue) or any other

materials and biotechnologies to replace, reconstruct or regenerate a living tissue or organ and to restore a normal function. Dental and orofacial applications are numerous **[2,3]**, starting from dental pulp regeneration, preimplant bone regeneration to extended maxillofacial reconstruction. However the TERM concerns all medical specialties and is a major basic science domain also. As a domain of research in Life sciences, it is one of the best illustrations of the need for medical transdisciplinarity and translational research.

Medical transdisciplinarity is in the essence of the TERM, because the development and results obtained in one medical field (e.g. orthopedic surgery) have often a direct impact in many others (e.g. oral and maxillofacial surgery)**[4]**: for example bone materials, titanium screws and regenerative strategies developed for lower limb reconstruction can often be applied to oral smaller-sized regeneration (the contrary is maybe even more true). In the field of platelet concentrates for surgical use (commonly known as Platelet-Rich Plasma – PRP or Platelet-Rich Fibrin – PRF), the same (or similar) preparations can be used in general surgery **[5]**, ophthalmological surgery **[6]**, plastic surgery **[7]**, orthopedics **[8]**, sports medicine **[9]** or in oral and maxillofacial surgery **[10,11]**. The concepts of regenerative medicine have to be tailored and adjusted to each specialty, but any good publication in one medical domain concerns also the applications in the others.

Translational research is also the founding stone of the TERM, because applied tissue engineering implies the cooperation between basic researchers (material engineers, biologists, etc) and clinicians from all domains. For example, the development of new surfaces for implantable materials **[12]** requires engineers (very specialized such as surface specialists, metallurgists, etc), cell biologists for in vitro testing, sometimes veterinarians for animal investigations of applications, and finally a crowd of clinicians in Humans. When this translational cooperation is not respected, serious confusions can appear. For example, as it was advocated by several authors **[12,13]**, a large part of the literature testing various implant surfaces is significantly biased, as the tested surfaces were simply not characterized properly (or not characterized at all): if a tested product is not clearly define, the results are logically difficult to interpret. If we consider the expertise of surface engineers and the powerful instruments of evaluation available since years, it is surprising to observe such situation. In a series of 5 articles published recently **[13-17]**, it was shown the detailed surface characteristics of 62 implant surfaces available on the market, and all of them presented very different chemistry and topography, while it was the first time - for most products - that these data were so clearly shown and spelled. This example in a very research-intensive field illustrates very well that the notion of translational approach and communication between basic scientists and applied scientists is very needed but still far from being optimal.

In fact, the integration of transdisciplinary (transversal) and translational (vertical) research is the founding need of the TERM. Shall we define this domain as a holistic discipline covering a large range of scientific domains (requiring therefore polyvalent researchers), or as a hub discipline connecting many specialists? Whatever the philosophical approach, this field is extremely multidisciplinary in its essence, and it requires for the team leaders to be able to navigate between the disciplines, vertically and transversally, to change permanently the standpoint to find new solutions to new problems.

This is on this conceptual basis that the PACT (Platelet & Advanced Cell Therapies) Forum Civitatis **(Figure)** of the POSEIDO Academic network **[18]** was designed, to support a multidisciplinary platform of research, publication, debates and eventually consensus for researchers from all disciplines working in this the field of tissue engineering and regeneration. The first objective of this multidisciplinary PACT, it is to support a more

ISSN 2307-5295, Published by the POSEIDO Organization & Foundation

holistic insight and original standpoints to get the right approach of the TERM. In this first PACT issue of the POSEIDO journal, a series of articles will illustrate very well this need.

Figure. The logo of the PACT (Platelet & Advanced Cell Therapies) Forum, representing the 3 components of a tissue in 3 colors (cells, matrix, mediators) and the lightning of Life, organized like a big P sealing this PACT.

2. A PACT for translational research and transdisciplinarity: the PRP case

Despite the strong interest and fashion for the TERM, the significant investments of the industry and public funding bodies since many years and the considerable literature, the direct clinical applications and results in this domain are still relatively limited and their impact quite modest. Many materials are working quite well, but it is finally more an Evolution than a Revolution. If we follow the developments in the last 10 years, it is an emerging field, and there is a risk that it may remain it for many more years.

The biggest issue in the development of this domain, it is frequently the lack of real conceptual and practical transdisciplinary and translational approach in the research groups. Research groups are often too specialized (in dentistry or other disciplines), and they are lacking the capacity or even the wish to integrate themselves in a more global multidisciplinary ensemble, even for treating complex topics that they do not have the full competence to even consider. In this sense, the literature about platelet concentrates for surgical use (PRP/PRF)**[19]** is a perfect example, as it is also probably the oldest method of regenerative medicine ever developed.

Platelet concentrates are autologous blood extracts prepared through centrifugation of a blood sample of the patient **[19]**. Whatever the method used, the objective of this technology is the same: to gather and collect the platelets (particularly rich in growth factors), the fibrinogen (later activated into a protective fibrin matrix supporting the healing process) and in some cases the cell content (particularly some populations of leukocytes), and to inject or place this preparation into a wounded or surgical site to improve healing and promote tissue regeneration. Historically, the use of this family of blood extracts started in

ISSN 2307-5295, Published by the POSEIDO Organization & Foundation

the 60-70's with the publications of Matras about fibrin glues **[20]**; it was tested in that time to cover and promote the healing of skin wounds and ulcers. This first approach of tissue regeneration is probably one of the oldest and founding methods of regenerative medicine. It was then mostly based on the concept of regeneration through the use of an autologous scaffold, the fibrin matrix being also the first matrix appearing in a wound after coagulation during a natural healing process **[21,22]**. Fibrin glues are still important surgical adjuvants nowadays.

In the following years, the combination of fibrin with platelets became more frequent, as a logical evolution of this technology, to reinforce the fibrin scaffold but also to use the expected healing properties of the platelets. Therefore, the history of this family of products continues with many tested applications of fibrin-platelet mixtures, tested with some success in neurosurgery **[23]**, ophthalmology **[24]**, general surgery **[25]** and plastic surgery **[26]**, even if these technologies were not widely spread. These products illustrated one of the first forms of regenerative medicine strategies applied to many different medical fields, and they highlighted – more than 40 years ago – the obvious need for medical transdisciplinarity.

The real craze for these technologies developed brutally in the last 15 years, when the concept of "growth factors" was spelled and promoted **[27]**: the early concepts of regenerative medicine (through a coherent fibrin scaffold reinforced with platelet aggregates) were substituted – in the heads of too many researchers – by a pharmacological concept, where a few selected growth factors were expected to regenerate tissues **[28]**. The Industry started to offer and promote many different and often expensive kits for the production of platelet concentrates. Many different techniques were regrouped by mistake under the general acronym PRP (Platelet-Rich Plasma)**[19]**. These technologies were tested in all medical fields even if the most frequent applications can be found in the literature in ophthalmological surgery **[6]**, plastic surgery **[7]**, orthopedics **[8]**, sports medicine **[9]** and particularly in oral and maxillofacial surgery **[10,11]**. As an innovative approach of regenerative medicine, all disciplines were again concerned by these technologies **[4]**. Expectations were very high, as much as the disappointment was a few years later. With a majority of the tested applications of PRP, results were mixed and controversial, and cost-effectiveness was weak. The literature remains very chaotic and difficult to sort and interpret **[28]**. The most logical explanation for this situation is that, despite the number of disciplines interested by the PRP technologies, very little transdisciplinarity could be really observed.

In many aspects, the domain of platelet concentrates is the nightmare of specialist researchers. To be able to apprehend correctly the complexity of blood extracts, serious competences in hematology, immunology, cell biology and endocrinology are needed (at least)**[29]**, as much as the medical and research knowledge of the clinical domains where these products are combined with specialized treatments into a regenerative medicine strategy. Unfortunately, most articles published by dental or orthopedic groups do not integrate a real multidisciplinary team, and the basic knowledge associated with the production of platelet concentrates was often neglected **[19]**. The most famous example was the confusion in the terminology, where all products were gathered under the acronym "PRP", while each protocol in fact leads to a very different combination of cells, matrix and factors **[19]**.

It required 10 years and many scientific debates before a more scientific vision of these materials was reformulated by a transdisciplinary and translational research team **[19,28,30]**: blood is a very complex circulating tissue, PRP and PRF are blood extracts, PRP and PRF are therefore living tissue grafts and not a pharmacological preparation. This aphorism is true in most cases, but it was particularly demonstrated with the L-PRF

ISSN 2307-5295, Published by the POSEIDO Organization & Foundation

(Leukocyte- and Platelet-Rich Fibrin) clots and membranes, as this material presents a very specific tissue architecture combining fibrin, platelets, circulating cells and all blood components **[31]**. It contains all the complexity of the blood tissue itself **[32]** and was often described as an "optimized blood clot".

To improve the terminology, platelet concentrates were regrouped in 4 big families based on their cell content and fibrin architecture **[19]**: Pure Platelet-Rich Plasma (P-PRP), Leukocyte- and Platelet-Rich Plasma (L-PRP), Pure Platelet-Rich Fibrin (P-PRF), Leukocyte- and Platelet-Rich Fibrin (L-PRF). This major classification is widely cited and serves already as guidelines of the POSEIDO community in this field **[33]**. Thanks to this transdisciplinary and translational approach, the perception of the topic by the scientific community is slowly evolving, even if confusions are still very frequent: there is no Magic of "growth factors", platelet concentrates are in fact very complex autologous tissue grafts and must be very well characterized before they are tested.

Unfortunately, the absence of holistic approach of the topic marked the literature on platelet concentrates with major confusion and illusion of knowledge, the most terrible legacy in Sciences. During many years – and still now – the exact cell content and fibrin architecture of tested platelet concentrates were not clearly characterized, and the most basic information about tested PRP/PRF was missing in most articles; as a consequence, a significant part of the literature on the topic is very difficult to interpret and was called sometimes a "blind library of knowledge" **[19,33]**.

This need for a deep transdisciplinarity and translational approach in the field of platelet concentrates is still extremely strong, as it is very clearly demonstrated by the articles composing this first PACT issue of the POSEIDO Journal. In fact, in many aspects, it is still just starting and this issue is bringing some major breakthrough in the understanding of the field.

3. A PACT against the Merchants to better serve the People and the Industry

Another main issue impacting negatively the development of the field, it may be the huge expectations from funding bodies and the industry in this domain. As tissue engineering and regenerative medicine became much more than just a domain of research – it is almost a Craze – huge resources were invested in a quite short period, stimulating a large literature in all aspects and a need to bring some outcomes from it. This pressure – academic, industrial, mediatic – is a supplementary burden, and it is often pushing scientists to stay even more strictly in one path, and blocking them mentally and financially to take more innovative and risky paths or to go for real debates on the issues encountered in the field.

The field of platelet concentrates is again an excellent illustration of how the commercial and the peer pressure can destroy an outstanding innovative domain. While various platelet gels were tested quietly and with success since many years – a long history started with the work of Matras more than 45 years ago **[20]** – the "Craze for Growth Factors" launched in 1998 **[27]** triggered a massive investment from companies and funding bodies into the field of the PRP-type products. In a few years, many expensive kits and devices were marketed and promoted, and the number of publications on this matter exploded. But with this sudden commercial pressure, scientific communities did not get the possibility to develop the proper concepts and understanding of these techniques. As previously explained, a large part of the literature is incomplete and almost unusable in this field **[19]**.

ISSN 2307-5295, Published by the POSEIDO Organization & Foundation

The worst consequence was probably the impact of this commercial pressure on the community of users. The PRP fashion was initially very strong (commercially and scientifically) in the domain of oral and maxillofacial surgery, and PRP products were very strongly advertised in all dental meetings. These techniques were in most cases expensive, cumbersome and time-consuming, and the commercial pressure promoting these technologies was in general much higher than the real clinical benefits the practitioners could observe in their patients in their daily practice. The benefit/cost ratio appeared very weak for most users, and the decline of these technologies was very quick. When walking through a dental meeting nowadays, it is easy to observe that PRP technology has almost completely disappeared from the domain. In many countries and communities, platelet concentrate technologies became a source of jokes about the craze for growth factors, or at least a topic considered as not significant. The chaotic literature and the commercial pressure for these products almost discredited these technologies in oral and maxillofacial surgery **[34]**.

In oral surgery, the main platelet concentrate still used, and strongly developing since a few years, is the L-PRF family (Leukocyte- and Platelet-Rich Fibrin)**[19]**. This method appeared very simple, inexpensive and user-friendly, while promoting obvious clinical results justifying very clearly its use **[10]**. The irony of the situation is that this method was developed by a group of clinicians – not by Academic teams nor by the Industry – and was designed as an open-access method, even if some CE/FDA cleared and optimized materials are now available (Intra-Spin L-PRF, Intra-Lock, Boca-Raton, FL, USA)**[33]**. It is expected that it will be the main method of platelet concentrates that will survive in the oral and maxillofacial field, and most probably become also a common gold standard to use in many oral surgical procedures.

However, the relative failure of the early PRP technologies in the oral and maxillofacial field had and still has a very negative impact in the development of other more efficient techniques such as L-PRF. Researchers on L-PRF spent a considerable time in the last 14 years just to repeat and clarify that PRF and PRP are 2 different families of products **[19]**, even if it is obvious when simply observing the products: PRP are liquid solutions that can be softly gelified like fibrin glues, while PRF families only exist as strong fibrin/platelets clots and membranes. It affected also the possibility of publications about these techniques, as the confusion between PRP and PRF was and still remains strong for reviewers and specialists. After the craze for growth factors and the commercial pressure, the suspicion and disinterest towards these technologies was so strong, that it affected even open-access cost-effective technologies that were providing obvious very efficient results. When the discredit touches a field, it concerns the whole field and for a long period. The short-term commercial vision promoted by “Merchants” finally provoked its contrary effects on the long-term **[34]**. Clarity, non-commercial works and cooperation are vital to serve adequately the patients, the research community and the Industry.

A second good example is implant surface design. In theory, the development of new nanomodified surfaces – with specific nanodesign, chemical modification or simply with new micropatterns - was claimed by all specialists to be the future of the field **[35,36]**, to improve even more the quality of osseointegration of the bone implantable materials. Practically speaking, despite the huge literature and investments of the funding bodies and companies, most companies are still using some very basic and quite old surface treatments, as it was clearly shown recently in the ISIS (Implant Surface Identification Standard) project of the POSEIDO network **[13]**: a majority of variations of the SLA-type surfaces (Sand-blasted, Large-grit, Acid-etched)**[15]** or RBM-type surfaces (Resorbable Blasting Media)**[16]**, and a few other minor types (anodized, titanium-plasma sprayed and various forms of coatings

ISSN 2307-5295, Published by the POSEIDO Organization & Foundation

with calcium phosphates)**[14,17]**. Most companies refuse to use experimental approaches promoted in the literature **[37]**, as the implementation of a new scientific fashion in this domain lead historically several times into significant industrial disappointments **[38]**. In a field where more than 95% of success can be reached by trained surgeons, companies have understood that it is more worthy – and less risky – to use efficient classical surface treatments and to invest in clinical education and surgeon training, than to believe in the miracles of tissue engineering. Some real innovations and improvements are still possible and some families of products such as the SIMN (Subtractive Impregnated Micro/Nanotextured)**[16]** surfaces are opening huge opportunities in surface-led tissue engineering **[39]**; however the commercial and academic pressure in this field in the last 15 years has already damaged significantly this topic. The early craze and excess in this field will impact negatively future major developments during several years: it is clearly negative for patients, scientists and also for the Industry, all stakeholders missing real existing opportunities **[39]** because of short-term illusions.

What happened to the fields of PRPs or implant surfaces may happen to many other branches of tissue engineering and regenerative medicine. The threat is always that results do not meet the expectations quickly enough; in the absence of concrete major results despite the quantity of money invested in the domain by various funding bodies (particularly companies) and sometimes the users, a domain loses its interest before arriving to maturation. As a paradoxical counterproductive effect, an excessive commercial, mediatic or academic pressure to obtain short-term benefits is often the source of commercial confusions and damaging the long-term potential of a whole domain, finally impacting negatively patients, users, scientists and the Industry itself. These examples shall always be kept in mind by researchers and industrials in the field. Like a financial speculative bubble, when a bubble of investment explodes, confusions and failures have global and lasting consequences for all stakeholders.

Platelet concentrates are still very useful technologies if they are selected and used adequately **[7]**; L-PRF has now a considerable impact worldwide in oral surgery **[10,11]**, and this inexpensive user-friendly method is clearly serving the patient and clinician interests. The potential of these blood extracts is still considerable for the industry **[4]**, as it concerns all medical domains, particularly orthopedics and sports medicine **[40]**. The concept of the PACT is not to keep the Industry out of the Community. However a serious Industry needs long-term vision to get long-term stability and benefits - and not short-term minor commercial gains - and to be really efficient and productive for the Communities of Scientists and Patients. This need for clear, honest, transparent, open-minded, non commercial approach **[34]** is the heart of the PACT Forum, and is serving the long-term interests of all stakeholders. In a fashionable research domain such as tissue engineering and regenerative medicine, care must be taken permanently to keep Merchant behaviors out of the scientific Temple. It is our PACT.

4. A PACT against the illusion of knowledge

The interferences of the funding bodies and the Merchant behaviors are often hiding a last threat, much deeper and more insidious: our certitudes, our beliefs. And platelet concentrates and regenerative medicine are very good examples of domains with people "believing in it or not" – a kind of faith, far from what the scientific open, curious and permanently inquiring mind should be.

ISSN 2307-5295, Published by the POSEIDO Organization & Foundation

Daniel J. Boorstin, a modern American historian who served also as Librarian of U.S. Congress, wrote that the history of Western science confirms the aphorism that the great menace to progress is not ignorance but the illusion of knowledge. The "aphorism" in question was formulated frequently in philosophical history, starting by Socrates in the Antique times. Boorstin spelled this idea repetitively and in many different forms in his books, but we voluntarily selected this version, referring explicitly to the Western science.

Indeed, even if the need for transdisciplinarity and translational approach appears obvious for most scholars, there is another need, which is very often neglected, or misunderstood: this is the need for international – we could even write intercultural – cooperation in this domain. The fact that some countries may appear more developed in sciences - in theory - is often for them the main blockage to consider another standpoint. In Science, certitudes are the worst enemies of Progress, and the Philosophers of Science always insist that the only absolute Truth, it is that there is no absolute Truth. In Science, the perception, understanding and interpretation of a scientific domain (and of the related industry for example) are strongly impacted by cultural parameters (including the perception of social needs and the relationships with the industry). This is often a limit in cooperation. But it can also be a chance, as it opens the possibility to see a problem from different standpoints, and find surprising solutions. More generally, the aphorism repeated so frequently by Boorstin recalls us that a real Scientist shall avoid to be stuck on certitudes and trapped by protective self-fulfilling illusions.

In this first PACT issue of the POSEIDO journal, a series of articles were selected. These articles have one particularity: they demonstrate that the majority of the literature in the field of platelet concentrates for surgical use presents major flaws. In daily practice, investigators observed considerable clinical differences between various platelet concentrate procedures, but the real biological mechanisms remained largely unclear up to now **[41]**; these articles provide a quite unique insight of the complexity of the problem. These articles are both translational and transdisciplinary, as they required the cooperation between engineers, biologists, hematologists, dental and orthopedic specialists. Even if these articles are not directly about clinical results, they are directly tied with the observations of clinicians using these materials.

The first article highlights for the first time the huge diversity of cells present in a small volume of Leukocyte- and Platelet-Rich Plasma (L-PRP) solution. It confirms the major flaw in all articles that did not consider the impact of the cell content on the biology of the platelet concentrates (as the majority of PRPs are in fact L-PRP)**[42]**; it confirms even more clearly that PRPs are not pharmaceutical preparations, but a real autologous tissue graft.

The following series of 3 articles highlights for the first time the impact of the centrifuge characteristics on the cell content and organization of a PRF clot, using the well-identified standard L-PRF protocol as the reference point **[31]**. This study demonstrates that the centrifuge type and vibrations have a considerable impact on the production of PRP/PRF. It reveals this major missing parameter and potential flaw in most publications on platelet concentrates, as many authors are using many different centrifuges without investigating the effect of their devices on their preparations. Finally, the evaluation of the biological signature (in terms of growth factors)**[41]** of different PRF clots obtained with slightly different protocols reveals the considerable impact of tiny protocol changes on the biological patterns of these materials. This issue is both a destructive stone for the literature in the field and a founding stone for a better research in this topic.

ISSN 2307-5295, Published by the POSEIDO Organization & Foundation

5. Perspectives

The PACT Forum logo **(Figure)** is made of 3 circles representing the traditional 3 components of a tissue: cells, matrix and mediators. The same concept is the basis of the tissue engineering perspective, where researchers always try to combine cells, scaffolds and bioactive molecules. The lightning symbol represents the combination of these 3 components placed into action. It can be seen as the blood support and the integration into the living tissues in vivo, or as the artificial methods to give life to the engineered tissues in vitro. Behind this general symbolism, the notion of scientific PACT itself is very important, when considering the general situation of this field. In this sense, the PACT represents also the need to seal this agreement within our community. It is a PACT to debate and to cooperate freely with an open mind and a long-term vision, a PACT to promote new approach and innovative standpoints, and a PACT to invent new perspectives and solutions to the problems the domain is facing, through trans-disciplinarity, translational research and international cooperation. It is also a PACT of transparency and clarity for the future of the field, far from commercial pressures and keeping Merchant behaviors out of our Temple. This is the PACT offered to the POSEIDO community, and on this PACT we hope to build our Future. There is no better symbol for all these expectations than the Lightning, the power of the innovative idea of the imaginative mind, which suddenly changes the Darkness into Light.

Disclosure of interests

The authors have no conflict of interest to report.

Acknowledgements

This work for the definition of international standards in implantable materials, tissue engineering and regenerative medicine is supported by a grant from the National Research Foundation of Korea (NRF) funded by the Korean government- MEST (No. 2011-0030121) and by the LoB5 Foundation for Research, France.

References

[1] Horch RE, Kneser U, Polykandriotis E, Schmidt VJ, Sun J, Arkudas A. *Tissue engineering and regenerative medicine -where do we stand?* **J Cell Mol Med**. 2012;16(6):1157-65.

[2] Mao JJ, Giannobile WV, Helms JA, Hollister SJ, Krebsbach PH, Longaker MT, Shi S. *Craniofacial tissue engineering by stem cells*. **J Dent Res**. 2006;85(11):966-79.

[3] Ramseier CA, Rasperini G, Batia S, Giannobile WV. *Advanced reconstructive technologies for periodontal tissue repair*. **Periodontol 2000**. 2012;59(1):185-202.

[4] Bielecki T, Dohan Ehrenfest DM. *Platelet-rich plasma (PRP) and Platelet-Rich Fibrin (PRF): surgical adjuvants, preparations for in situ regenerative medicine and tools for tissue engineering*. **Curr Pharm Biotechnol**. 2012;13(7):1121-30.

[5] Everts PA, Hoogbergen MM, Weber TA, Devilee RJ, van Monftort G, de Hingh IH. *Is the use of autologous platelet-rich plasma gels in gynecologic, cardiac, and general, reconstructive surgery beneficial?* **Curr Pharm Biotechnol**. 2012;13(7):1163-72.

[6] Alio JL, Arnalich-Montiel F, Rodriguez AE. *The role of "eye platelet rich plasma" (E-PRP) for wound healing in ophthalmology*. **Curr Pharm Biotechnol**. 2012;13(7):1257-65.

[7] Cieslik-Bielecka A, Choukroun J, Odin G, Dohan Ehrenfest DM. *L-PRP/L-PRF in esthetic plastic surgery, regenerative medicine of the skin and chronic wounds*. **Curr Pharm Biotechnol**. 2012;13(7):1266-77.

[8] Yuan T, Guo SC, Han P, Zhang CQ, Zeng BF. *Applications of leukocyte- and platelet-rich plasma (L-PRP) in trauma surgery*. **Curr Pharm Biotechnol**. 2012;13(7):1173-84.

[9] Mishra A, Harmon K, Woodall J, Vieira A. *Sports medicine applications of platelet rich plasma*. **Curr Pharm Biotechnol**. 2012;13(7):1185-95.

ISSN 2307-5295, Published by the POSEIDO Organization & Foundation

[10] Del Corso M, Vervelle A, Simonpieri A, Jimbo R, Inchingolo F, Sammartino G, Dohan Ehrenfest DM. *Current knowledge and perspectives for the use of platelet-rich plasma (PRP) and platelet-rich fibrin (PRF) in oral and maxillofacial surgery part 1: Periodontal and dentoalveolar surgery*. **Curr Pharm Biotechnol**. 2012;13(7):1207-30.
[11] Simonpieri A, Del Corso M, Vervelle A, Jimbo R, Inchingolo F, Sammartino G, Dohan Ehrenfest DM. *Current knowledge and perspectives for the use of platelet-rich plasma (PRP) and platelet-rich fibrin (PRF) in oral and maxillofacial surgery part 2: Bone graft, implant and reconstructive surgery*. **Curr Pharm Biotechnol**. 2012;13(7):1231-56.
[12] Dohan Ehrenfest DM, Coelho PG, Kang BS, Sul YT, Albrektsson T. *Classification of osseointegrated implant surfaces: materials, chemistry and topography*. **Trends Biotechnol**. 2010;28(4):198-206.
[13] Dohan Ehrenfest DM, Del Corso M, Kang BS, Leclercq P, Mazor Z, Horowitz RA, Russe P, Oh HK, Zou DR, Shibli JA, Wang HL, Bernard JP, Sammartino G. *Identification card and codification of the chemical and morphological characteristics of 62 dental implant surfaces. Part 1: description of the Implant Surface Identification Standard (ISIS) codification system*. **POSEIDO**. 2014;2(1):7-22.
[14] Dohan Ehrenfest DM, Del Corso M, Kang BS, Leclercq P, Mazor Z, Horowitz RA, Russe P, Oh HK, Zou DR, Shibli JA, Wang HL, Bernard JP, Sammartino G. *Identification card and codification of the chemical and morphological characteristics of 62 dental implant surfaces. Part 2: anodized and Titanium Plasma-Sprayed (TPS) surfaces (Group 1, metallurgy modification)*. **POSEIDO**. 2014;2(1):23-35.
[15] Dohan Ehrenfest DM, Del Corso M, Kang BS, Leclercq P, Mazor Z, Horowitz RA, Russe P, Oh HK, Zou DR, Shibli JA, Wang HL, Bernard JP, Sammartino G. *Identification card and codification of the chemical and morphological characteristics of 62 dental implant surfaces. Part 3: sand-blasted/acid-etched (SLA type) and related surfaces (Group 2A, main subtractive process)*. **POSEIDO**. 2014;2(1):37-55.
[16] Dohan Ehrenfest DM, Del Corso M, Kang BS, Leclercq P, Mazor Z, Horowitz RA, Russe P, Oh HK, Zou DR, Shibli JA, Wang HL, Bernard JP, Sammartino G. *Identification card and codification of the chemical and morphological characteristics of 62 dental implant surfaces. Part 4: Resorbable Blasting Media (RBM), Dual Acid-Etched (DAE), Subtractive Impregnated Micro/Nanotextured (SIMN) and related surfaces (Group 2B, other subtractive process)*. **POSEIDO**. 2014;2(1):57-79.
[17] Dohan Ehrenfest DM, Del Corso M, Kang BS, Leclercq P, Mazor Z, Horowitz RA, Russe P, Oh HK, Zou DR, Shibli JA, Wang HL, Bernard JP, Sammartino G. *Identification card and codification of the chemical and morphological characteristics of 62 dental implant surfaces. Part 5: chemically coated surfaces (Group 3, coating) and implant collar surfaces (Group 4, collar)*. **POSEIDO**. 2014;2(1):81-104.
[18] Dohan Ehrenfest DM, Sammartino G, Bernard JP. *The Periodontology, Oral Surgery, Esthetic and Implant Dentistry Organization (POSEIDO) and Open Journal: an international academic and scientific community for a new approach of open-access publishing*. **POSEIDO**. 2013;1(1):1-5.
[19] Dohan Ehrenfest DM, Rasmusson L, Albrektsson T. *Classification of platelet concentrates: from pure platelet-rich plasma (P-PRP) to leucocyte- and platelet-rich fibrin (L-PRF)*. **Trends Biotechnol**. 2009;27(3):158-67.
[20] Matras H. *Die Wirkungen vershiedener Fibrinpraparate auf Kontinuitat-strennungen der Rattenhaut*. **Osterr Z Stomatol**. 1970;67(9):338-59.
[21] Clark RA. *Fibrin and wound healing*. **Ann N Y Acad Sci**. 2001;936(355-67.
[22] Gibble JW, Ness PM. *Fibrin glue: the perfect operative sealant?* **Transfusion**. 1990;30(8):741-7.
[23] Silverberg GD, Harbury CB, Rubenstein E. *A physiological sealant for cerebrospinal fluid leaks*. **J Neurosurg**. 1977;46(2):215-9.
[24] Rosenthal AR, Harbury C, Egbert PR, Rubenstein E. *Use of a platelet-fibrinogen-thrombin mixture as a corneal adhesive: experiments with sutureless lamellar keratoplasty in the rabbit*. **Invest Ophthalmol**. 1975;14(11):872-5.
[25] Pearl RM, Wustrack KO, Harbury C, Rubenstein E, Kaplan EN. *Microvascular anastomosis using a blood product sealant-adhesive*. **Surg Gynecol Obstet**. 1977;144(2):227-31.
[26] Knighton DR, Ciresi KF, Fiegel VD, Austin LL, Butler EL. *Classification and treatment of chronic nonhealing wounds. Successful treatment with autologous platelet-derived wound healing factors (PDWHF)*. **Ann Surg**. 1986;204(3):322-30.
[27] Marx RE, Carlson ER, Eichstaedt RM, Schimmele SR, Strauss JE, Georgeff KR. *Platelet-rich plasma: Growth factor enhancement for bone grafts*. **Oral Surg Oral Med Oral Pathol Oral Radiol Endod**. 1998;85(6):638-46.
[28] Dohan Ehrenfest DM, Bielecki T, Mishra A, Borzini P, Inchingolo F, Sammartino G, Rasmusson L, Evert PA. *In search of a consensus terminology in the field of platelet concentrates for surgical use: platelet-rich plasma (PRP), platelet-rich fibrin (PRF), fibrin gel polymerization and leukocytes*. **Curr Pharm Biotechnol**. 2012;13(7):1131-7.

ISSN 2307-5295, Published by the POSEIDO Organization & Foundation

[29] Borzini P, Balbo V, Mazzucco L. *Platelet concentrates for topical use: bedside device and blood transfusion technology. Quality and versatility*. **Curr Pharm Biotechnol**. 2012;13(7):1138-44.
[30] Dohan Ehrenfest DM, Andia I, Zumstein MA, Zhang CQ, Pinto NR, Bielecki T. *Classification of platelet concentrates (Platelet-Rich Plasma-PRP, Platelet-Rich Fibrin-PRF) for topical and infiltrative use in orthopedic and sports medicine: current consensus, clinical implications and perspectives*. **Muscles Ligaments Tendons J**. 2014;4(1):3-9.
[31] Dohan Ehrenfest DM, Del Corso M, Diss A, Mouhyi J, Charrier JB. *Three-dimensional architecture and cell composition of a Choukroun's platelet-rich fibrin clot and membrane*. **J Periodontol**. 2010;81(4):546-55.
[32] Dohan Ehrenfest DM, Diss A, Odin G, Doglioli P, Hippolyte MP, Charrier JB. *In vitro effects of Choukroun's PRF (platelet-rich fibrin) on human gingival fibroblasts, dermal prekeratinocytes, preadipocytes, and maxillofacial osteoblasts in primary cultures*. **Oral Surg Oral Med Oral Pathol Oral Radiol Endod**. 2009;108(3):341-52.
[33] Dohan Ehrenfest DM, Sammartino G, Shibli JA, Wang HL, Zou DR, Bernard JP. *Guidelines for the publication of articles related to platelet concentrates (Platelet-Rich Plasma - PRP, or Platelet-Rich Fibrin - PRF): the international classification of the POSEIDO*. **POSEIDO**. 2013;1(1):17-27.
[34] Dohan Ehrenfest DM, Bielecki T, Del Corso M, Inchingolo F, Sammartino G. *Shedding light in the controversial terminology for platelet-rich products: platelet-rich plasma (PRP), platelet-rich fibrin (PRF), platelet-leukocyte gel (PLG), preparation rich in growth factors (PRGF), classification and commercialism*. **J Biomed Mater Res A**. 2010;95(4):1280-2.
[35] Mendonca G, Mendonca DB, Aragao FJ, Cooper LF. *Advancing dental implant surface technology--from micron- to nanotopography*. **Biomaterials**. 2008;29(28):3822-35.
[36] Shibli JA, Dohan Ehrenfest DM. *In dental implant surfaces, NanoWar has begun... but NanoQuest is still at stake!* **POSEIDO**. 2013;1(3):131-40.
[37] Dohan Ehrenfest DM, Rutkowski JL. *Evolution of the dental implant market: an African tale revisited*. **J Oral Implantol**. 2012;38(3):201-2.
[38] Abrahamsson I, Linder E, Larsson L, Berglundh T. *Deposition of nanometer scaled calcium-phosphate crystals to implants with a dual acid-etched surface does not improve early tissue integration*. **Clin Oral Implants Res**. 2013;24(1):57-62.
[39] Coelho PG, Granato R, Marin C, Bonfante EA, Freire JN, Janal MN, Gil JN, Suzuki M. *Biomechanical evaluation of endosseous implants at early implantation times: a study in dogs*. **J Oral Maxillofac Surg**. 2010;68(7):1667-75.
[40] Zumstein MA, Berger S, Schober M, Boileau P, Nyffeler RW, Horn M, Dahinden CA. *Leukocyte- and platelet-rich fibrin (L-PRF) for long-term delivery of growth factor in rotator cuff repair: review, preliminary results and future directions*. **Curr Pharm Biotechnol**. 2012;13(7):1196-206.
[41] Dohan Ehrenfest DM, Bielecki T, Jimbo R, Barbe G, Del Corso M, Inchingolo F, Sammartino G. *Do the fibrin architecture and leukocyte content influence the growth factor release of platelet concentrates? An evidence-based answer comparing a pure platelet-rich plasma (P-PRP) gel and a leukocyte- and platelet-rich fibrin (L-PRF)*. **Curr Pharm Biotechnol**. 2012;13(7):1145-52.
[42] Bielecki T, Dohan Ehrenfest DM, Everts PA, Wiczkowski A. *The role of leukocytes from L-PRP/L-PRF in wound healing and immune defense: new perspectives*. **Curr Pharm Biotechnol**. 2012;13(7):1153-62.

This article can be cited as:
Sammartino G, Del Corso M, Wisniewska LM, Bielecki T, Andia I, Pinto NR, Zhang CQ, Zou DR, Dohan Ehrenfest DM. *The PACT (Platelet & Advanced Cell Therapies) Forum: fostering translational research, transdisciplinarity and international collaboration in tissue engineering and regenerative medicine.* **POSEIDO**. 2014;2(2):105-15.